

STUDY PROTOCOL

Title of the study: The efficacy of Rivaroxaban with Diosmine in the long-term treatment of acute proximal deep vein thrombosis

Brief title: Rivaroxaban With Diosmine in Long-term Treatment of DVT (RIDILOTT-DVT)

Sponsor: Pirogov Russian National Research Medical University

Clinical center: Clinical Hospital no.1 of the President's Administration of Russian Federation

Principle Investigator: Associated professor Ilya Schastlivtsev

Term of execution: 2018-2019

Th aim: to evaluate the efficacy of using disomine in combination with rivaroxaban compared with the isolated use of rivaroxaban during long-term treatment of acute proximal deep vein thrombosis.

Study design: a single-center open-label randomized clinical trial with blinded outcome assessor

Inclusion and exclusion criteria

Inclusion criteria:

- Age over 18 years
- The first episode lower limb DVT
- The absence or presence of clinical provocation of DVT (except active oncological process)
- Thrombosis verification using duplex scan
- Localization of thrombotic occlusion not below the popliteal vein and not above the inguinal fold
- Signed informed consent to participate in the study

Exclusion criteria:

- Suspicion of pulmonary embolism
- Verified pulmonary embolism
- Bilateral DVT
- Contraindications to the use of rivaroxaban (in accordance with the official instructions)

- Contraindications to the use of Diosmin (in accordance with the official instructions)
- Active oncological process
- Verified severe thrombophilia (APS, AT-3, protein C, S deficiency)
- The use of other anticoagulants for more than 7 days from the time of DVT verification
- The inability to use compression stockings after 3 days from the time of DVT verification
- Performed surgery on superficial or deep veins of the lower extremities (thrombolysis, thrombectomy, vein ligation, cava filter implantation)
- Constant use of other drugs that affect the hemostasis system (except for ASA in a dose of not more than 100 mg).
- Low compliance

Methods of diagnostic

The initial examination of patients with suspected DVT will be carried out within the first 4 hours after admission to the hospital and will include a physical examination to determine the clinical signs of acute deep vein thrombosis of the lower extremities, as well as all possible individual risk factors for venous thromboembolic complications. The integral clinical probability for DVT will be determined using a two-level Wells scale. If there is a high clinical probability for DVT duplex ultrasound scan (DUS) will be performed to verify the diagnosis. If there is a low clinical probability for DVT, the D-dimer level will be measured, if it is found to be elevated it will be followed by DUS. If an DVT is identified by DUS, its initial characteristics will be recorded in a special card (Appendix 1).

If a patient meets the inclusion and exclusion criteria, as well as after he signed the informed consent, he will be randomly assigned to the main or control group. If the patient is unconscious, informed consent may be signed by the patient's authorized person (immediate family).

Methods of randomization

The randomization will be performed by number of medical record: if the last digit is even - the patient is included in the main group, odd - in the control, zero - the previous digit is taken into account.

Methods of treatment

In both groups, standard conservative treatment for DVT will be conducted, including the use of rivaroxaban in a dosage of 15 mg twice daily for 3 weeks with a further transition to a single dose of 20 mg once daily. During the initial therapy for DVT will be allowed to use parenteral anticoagulants up to 7 days. All patients will not be allowed to use other drugs that affect the blood coagulation system, except of acetylsalicylic acid (ASA) in a dose of not more than 100 mg / day. Also, all patients

require to receive compression stockings of 20-30 mm of Hg within 3 days after DVT verification.

In the *control group*, only standard conservative treatment, including rivaroxaban and compression stockings, will be used. The anticoagulation with rivaroxaban will be stopped at 6 months, and the use of compression stockings will be prescribed up to 12 months.

In the *main group*, in addition to the standard treatment (rivaroxaban for 6 months and elastic compression stockings for 12 months), the Diosmin will be used at a dose of 600 mg (Phlebodia 600) once daily in a continuous mode for the entire 12 months.

Early termination of treatment and the withdrawal of patients from the study is possible due to the development of serious adverse events and complications of therapy (major bleeding, clinically relevant non-major bleeding, which required temporary discontinuation of the drug), as well as gross violations of compliance. In the event of minor and minor, but clinically significant bleeding that does not require discontinuation of drugs, the patient will be monitored as part of the study.

Follow up

Patients will be followed up to 12 months with monthly clinical examination to identify possible complications of therapy, a violation of the regimen of medication and a compliance with the elastic compression protocol. Also, every 2 months, a DUS will be performed according to the protocol with the results recorded in a specially designed map (Appendix 1).

At 6 and 12 months the presence and severity of the PTS by the Villalta scale, the severity of CVD by the rVCSS scale and the quality of life according to the CIVIQ-20 questionnaire (Appendix 2) will be assessed. Also, after 12 months, the final DUS will be performed to assess the final degree of recanalization. The nature of the activities carried out with the dynamic observation of the patient is presented in Table 1.

DUS will be performed before the patient is included in the study and then every 2 months throughout the entire treatment period. The study will include a graphical depiction of the thrombus burden, the distal and proximal thrombus border (in cm from the floor level), and the degree of recanalization of the venous segments. Recanalization of the venous segments will be assessed at three main levels: popliteal vein, femoral vein, common femoral vein, based on the degree of compressibility of the venous segment. The degree of compressibility of the venous segment will be calculated as the ratio of the difference between the diameter of the vein without compression and the diameter of the vein with maximum compression to the diameter of the vein without compression. For each venous segment, the degree of recanalization at the narrowest point will be taken into account.

Table 1. The content of follow-up

	Baseline	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m	11 m	12 m
Clinical investigation	+	+	+	+	+	+	+	+	+	+	+	+	+
DUS	+		+		+		+		+		+		+
Villalta							+						+
rVCSS							+						+
CIVIQ-20							+						+

Endpoints of the study

Primary efficacy endpoint: the frequency of PTS at 12 months by the Villalta scale (5 points or more).

Secondary efficacy endpoints:

- The severity of CVD by rVCC score at 6 and 12 months
- Quality of life by CIVIQ-20 at 6 and 12 months
- The degree of recanalization of the venous segments at 6 and 12 months of complex treatment
- Dynamics of recanalization of venous segments bi-monthly

Safety endpoints:

- Any adverse event (including overall mortality)
- Major adverse event (including major bleeding)
- Bleeding event:
 - Major bleeding by ISTH:
 - Recorded hemoglobin drop by more than 20 g/l
 - The need for blood transfusion of 2 or more doses of erythrocytes
 - Bleeding resulting in death
 - Bleeding in anatomically significant areas (brain, spinal cord, retroperitoneal space, pericardial cavity, joint cavity, intraocular, intermuscular hematoma)
 - Clinically relevant non-major bleeding: any bleeding that does not meet the criteria for major, but required the cancellation of the anticoagulant, and / or the implementation of hemostatic measures, and / or

hospitalization in the hospital, and / or unscheduled treatment to the doctor.

- Minor bleeding: any bleeding that does not meet the criteria of a major and/or CRNM, did not require the suspension of therapy and changes in the patient's lifestyle

Power calculations

The frequency of PTS detection in 12-24 months after verification of DVT is 20-50% (Kahn 2002). According to preliminary data, the use of Diosmin in combination with rivaroxaban compared to the isolated use of rivaroxaban for 12 months in patients with ileo-femoral thrombosis can reduce the severity of CVD symptoms by 1.5-2 times (Kuznetsov MR 2016). Thus, with the error of the first kind - 0.05 and the error of the second kind of 0.2, the initial 12-month incidence of PTS development at the level of 30% and its expected decrease by 3 times, the number of patients in two comparable groups should be 60 people, and total sample size - 120 patients. It is possible to complete the study earlier if the level of statistical significance of the differences obtained is reached. Intermediate statistical processing is planned for the recruitment of 30 patients each group.

A statistical analysis plan

Comparing the total frequency of occurrence of endpoints in the main and control groups using Fisher's exact test, comparing the probability of occurrence of endpoints over the observation period using Kaplan-Meier statistics, calculating the risk of developing PTS using Cox regression, comparing mean values of scoring systems for assessing the severity of the disease and quality of life using the t-test, comparing the dynamics of changes in the degree of recanalization by venous segments using general liner model for the repeated measures.

November 11, 2017

Principle investigator

Ilya Schastlivtsev

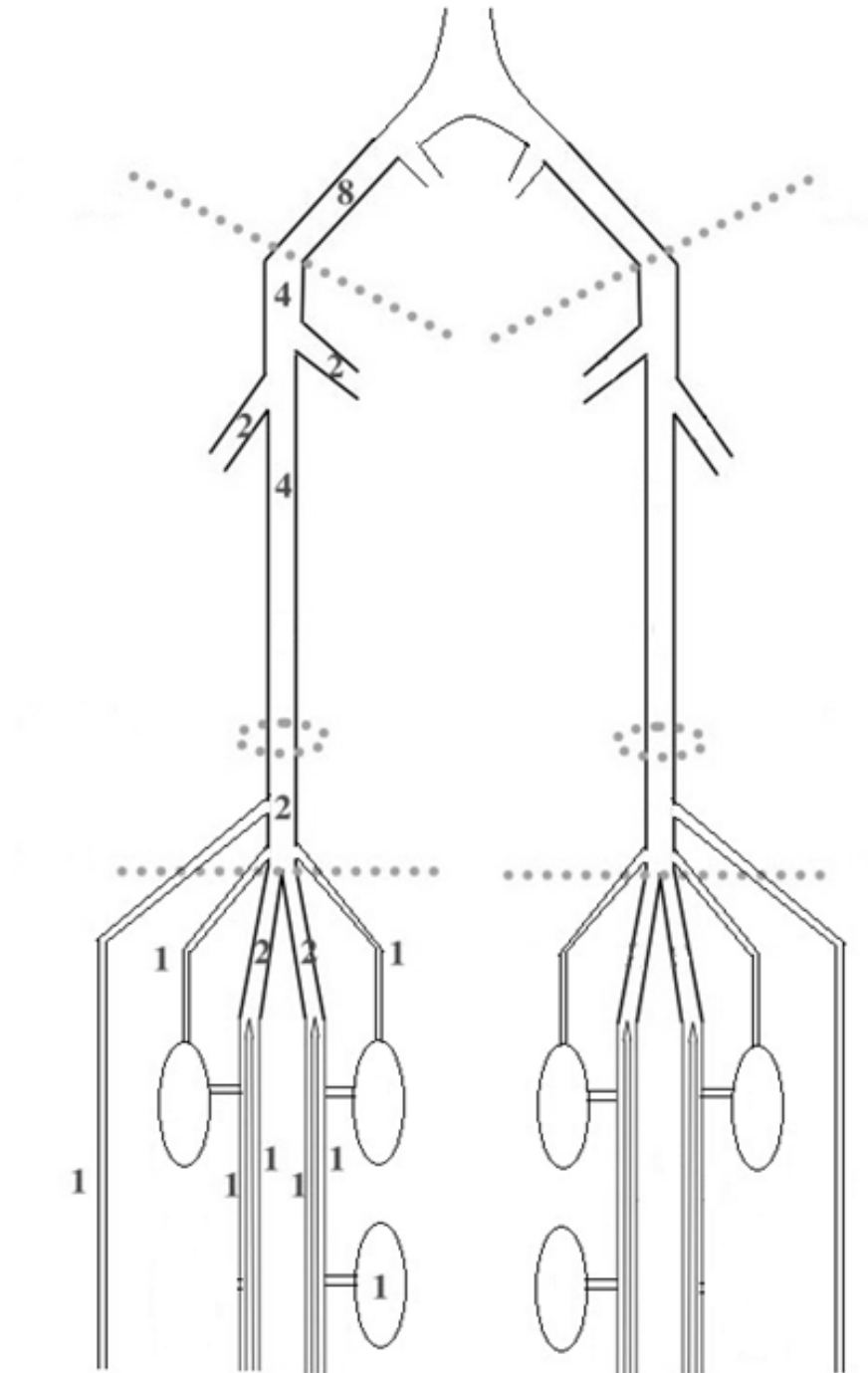


Duplex ultrasound scan

Date:

Name:

Age:



Conclusion: